PART 3. STUDY OF HOST FACTORS FOR CANCER AND THEIR INTERACTION WITH ENVIRONMENTAL FACTORS

3.1 Studies on the cytochrome P450 (Cyp) enzyme system and its role in carcinogenesis

3.1.1 Studies on structure–activity relationships of carcinogen-metabolizing cytochromes P450

Using recombinant yeasts constructed to express highly homologous mouse Cyp2a isozymes, we have shown that Cyp2a5 had a high affinity towards aflatoxin B_1 (AFB_1), while Cyp2a4 and Cyp7α, although almost identical to Cyp2a5, had a much lower affinity and metabolic capacity. Genetically engineered point mutations in Cyp2a5 cDNA, changing only one amino acid at a time, could drastically change its catalytic properties towards AFB_1.The sensitivity of the recombinant yeasts to AFB_1 and the binding of AFB_1 to the yeast DNA correlated very well with the K_m of the expressed Cyp isoform towards AFB_1 demonstrating a direct link between the affinity of the metabolizing enzyme to AFB_1 and the genotoxicity of AFB_1. It was concluded that Cyp2a5 is the principal isoenzyme that metabolizes AFB_1 within the Cyp2a subfamily and that the recombinant yeasts provide a good test system to analyse the roles of individual Cyp isoenzymes in AFB_1 toxicity (Pelkonen *et al.*, 1994).

3.1.2 Expression of cytochrome P450s in liver injury (p.131 of 1992/93 Biennial Report)

Chemically caused liver injury reduces total hepatic Cyp content but increases Cyp2a5 (Juvonen *et al.*, 1988; Pellinen *et al.*, 1993). Cyp2a5 metabolizes nitrosamines and aflatoxins (Camus *et al.*, 1993; see above). Therefore activation of some carcinogens might be increased in certain pathological conditions of the liver when their metabolism is catalysed by Cyp2a5. This hypothesis has been tested in three situations. First, increased expression of Cyp2a5 and related enzymatic activities after treatment of mice with chloroform and thioacetamide (two well known hepatotoxins) was demonstrated. This confirmed our previous results and suggests that structurally unrelated hepatotoxins may increase the expression of Cyp2a5. Second, using transgenic mice expressing hepatitis B virus (HBV) large envelope protein, which leads to alterations in the liver typical of hepatitis, we showed that Cyp2a5 expression and AFB_1 metabolism were increased in the liver compared with control mice. The increased expression

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of Cyp2a5 was associated with increased DNA binding of AFB_1 when mice were treated with AFB_1 (Kirby *et al.*, 1994) (see Section 2.11.4.1). Third, infestation of hamster with liver fluke (*Opisthorchis viverrini*) was shown to increase the expression of hepatic Cyp2a5 and the levels of nitrosamine and AFB_1 metabolism. The increased expression was strongest in areas of liver adjacent to the inflammation, where the highest levels of DNA-bound AFB_1 were also seen (Pelkonen *et al.*, 1993, 1994a; Kirby *et al.*, 1994).

These results show that Cyp2a5 expression is increased in various types of liver injury induced by chemicals, viruses or parasites, leading to enhancement of Cyp2a5-catalysed metabolism. This could provide one explanation for the synergistic effect of HBV and AFB_1 in hepatocarcinogenesis, and for other observed chemical–chemical, viral–chemical or parasite–chemical interactions in hepatocarcinogenesis (see Section 2.11.4).

The molecular mechanism of Cyp2a5 expression in relation to liver injury is largely unknown. In pyrazole-caused liver damage, we have found that mRNA stabilization (rather than stimulated transcription) may be important (Hahnemann *et al.*, 1992). Recently we have found that a 44 kDa protein induced by pyrazole binds specifically to the 3'-UTR of Cyp2A5 mRNA; this may have a role in the specific regulation of Cyp2a5 expression.

3.1 IARC staff publications

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3.2 Regulation of cellular response to DNA damage: studies of effects of DNA damage and repair on cell cycle control and carcinogenesis

3.2.1 **Control of expression of enzymes for DNA alkylation and oxidative damage repair during single and chronic exposures to carcinogens** (p. 133 of 1992/93 Biennial Report)

Alterations in the repair processes for methylated and oxidative DNA adducts have been found in rodent species following single or chronic exposure to *N*-nitrosodimethylamine (NDMA) and ionizing radiation. Distinct differences between rat and hamster have been noted in the modulation of liver O^6-alkylguanine-DNA-alkyltransferase (AGT), with a rapid increase in both mRNA and protein levels in rat liver but not in hamster liver following such treatments. In order to examine these changes at the cellular level *in situ*, hybridization techniques are being established. Preliminary experiments on the expression of the growth arrest and DNA damage inducible gene (gadd 45), which may be involved in signalling replication arrest, have shown that it is also rapidly induced in rat liver following similar carcinogen exposures; its expression in hamster liver is being investigated. Previous studies have demonstrated that environmental exposure to such agents results in the increase in the level of certain DNA repair enzymes such as the methylpurine-DNA glycosylase in smokers compared with non-smokers. We are now examining the distribution and the apparent induction of this enzyme in populations exposed to tobacco smoke (see also Section 2.4). (Financial support from the European Commission; contract no. EV5V-CT94-0401).

3.2.2 **DNA repair modulation by cellular injury** (p. 134 of 1992/93 Biennial Report)

The modulation of expression of the AGT repair protein by cellular injury resulting from inflammatory processes is being examined in experimental animal systems. No difference in hepatic AGT was noted in male or female hamster liver 12 weeks after infection with liver fluke (*Opisthorchis viverrini*), although this treatment produces alterations in other cellular defence systems such as cytochrome P450s (see Section 3.1). Preliminary experiments in rats treated intravenously with heat-killed *Propionibacterium acnes* followed by lipopolysaccharide (LPS) administration, which causes acute hepatic injury and induction of nitric oxide synthase (see Section 2.7), indicate a slight inhibition of AGT in treated animals (0.105 pmol/mg protein 8 hours after LPS administration, 0.132 pmol/mg protein in control liver). This result is in agreement with those of Laval and Wink, (1994), who demonstrated, using a nitric oxide-generating system in cultured cells, the inhibition of AGT activity.

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3.2.3 Regulation of the mammalian cellular response to DNA damage

The ataxia telangiectasia (AT) gene product has been implicated in the signal transduction pathway that causes a delay in cell cycle progression following exposure to ionizing radiation, together with the products of the tumour suppressor genes p21 and p53. Immunological and molecular biological techniques have been established to measure the expression of the p21 and p53 gene products and that of the gadd 45 and 153 genes. In some lymphoblastoid cell lines established from AT patients, p53 induction following exposure to ionizing radiation was reduced and/or delayed compared to the response in normal cells, whilst p53 induction following exposure to methyl methanesulfonate (MMS) in AT cell lines appeared to be as in the control cell lines. The increase in the level of gadd 45 mRNA following exposure to ionizing radiation was also reduced in AT cells compared with normal cells, confirming the data of Kastan's and Fornace's groups (Papathanasiou *et al.*, 1991; Kastan *et al.*, 1992), and suggesting that the responses to exposure to MMS and ionizing radiation are mediated via different pathways.

Preliminary experiments suggest that the changes in both the mRNA and protein levels of the tumour suppressor gene p21 following exposure to ionizing radiation parallel those observed for p53 induction in AT cells, providing additional evidence that the AT gene product is involved upstream of these two tumour-suppressor genes in the G1-S cell cycle block. These studies are being extended to patients with breast cancer, a disease in which the AT gene has been implicated as a predisposing gene. These studies are supported by grants from the European Commission (CT94-0581).

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3.3. Studies on genetic determinants of specific cancers

3.3.1 Studies on the X-linked lymphoproliferative syndrome (XLP) (p.135 of 1992/93 Biennial report)

Patients with the X-linked lymphoproliferative disease (XLP) who harbour interstitial deletions or chromosomal rearrangements are important resources in the isolation of the XLP gene. An XLP patient with a large deletion in Xq25 including the marker DXS100 has been

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identified (Skare *et al.*, 1993; Sylla *et al.*, 1993). The deletion has been estimated to cover about two megabase pairs (Mbp). cDNA clones obtained after screening of a human fetal cDNA library with cosmid clones deleted in this patient contained all repetitive sequences. cDNAs were also isolated after screening of the placental and brain cDNA libraries, using CpG-containing cosmid clones mapped on Xq24-q26. Physical mapping of these clones indicated that they were outside the deletion (therefore excluded as candidate genes for XLP) and they were mapped at Xq12-q13 and 14q11-q12.

In order to define a minimal interval region containing the XLP gene, an extensive screening of XLP patients with all the known markers deleted in the patient described above and with newly published probes mapped to the Xq24-q26 region was undertaken. A second XLP patient with a relatively small deletion was identified. Screening of YAC libraries with probes deleted in this small interval has enabled us to isolate several overlapping YACs covering the deletion. A cosmid ***contig*** (a series of overlapping cosmid clones) of the region will be also established. Genes isolated from these YAC and cosmid clones will be tested as possible genes of the XLP syndrome.

3.3.2 Multiple endocrine neoplasia type 2 (MEN 2) (p. 137 of 1992/93 Biennial report)

Following the publications of Mulligan *et al.* and Donis-Keller *et al.*, reporting germline mutations of the RET proto-oncogene as the molecular basis of inherited susceptibility to medullary thyroid cancer (MTC), our laboratory has been actively analysing our panel of families. By sequencing exons 10 and 11 of the RET proto-oncogene in 68 unrelated familial cases of MEN 2A and familial MTC (without phaeochromocytoma), germline mutations were identified in 98% of the MEN 2A families and 57% of the familial MTC cases. In 11 patients, we found a mutation in exon 10. In the remaining two cases, the mutation was located in exon 11.

All the genetic changes observed were missense mutations affecting one of three cysteine codons located in the extracellular domain of RET. The alterations identified in exon 11 invariably involved codon 634. Six different transitions or transversions were observed at this codon. The two most frequent were T to C and G to A transversions. The mutations identified in exon 10 affected codons 618 and 620. Segregation of mutant alleles with the disease was verified for a total of 40 families.

Despite sharing the same mutation at codon 634, 620 or 618, some families did not have the same haplotype in the RET region. Using four polymorphisms located either in the RET coding region or no further than 200 kb, we identified at least seven different haplotypes in the subgroup of families sharing the T to C transversion at codon 634. In the subgroup of

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in the subgroup of families sharing the T to C transversion at codon 634. In the subgroup of families sharing the G to A transversion at codon 634, at least four different haplotypes were found (Schuffenecker *et al.*, 1994).

When MEN 2B patients were analysed (the more severe form of MEN 2 associating MTC, phaeochromocytomas, schwannomas and a marfanoid appearance), a single point mutation at codon 918 leading to the replacement of a methonine by a threonine within the RET tyrosine kinase domain was identified, as in all other MEN 2B cases reported so far (Rossel *et al.*, 1994). This mutation was identified in 16 out of our 18 unrelated MEN 2B families analysed. In these families we were able to demonstrate that, in five cases, the mutation arose *de novo*, and in one kindred was coinherited with the disease. These results indicate that a unique mutation at codon 918 of the RET gene is the most prevalent genetic defect causing MEN 2B, but also that rare MEN 2B cases are associated with different mutations yet to be defined.

This project is now being phased out at IARC. The typing of families will continue in a hospital-based setting and attempts to elucidate the biological basis of predisposition will be pursued mainly in national laboratories. The resources collected in the framework of these studies will be made available to investigators on request.

3.3.3 Neurofibromatosis type 2 (p.137 of 1992/93 Biennial Report)

Following the identification of the NF2 gene (Rouleau *et al.*, 1993), the NF2 families we had collected have been analysed for germline mutation of the schwannoma gene. So far mutations have been identified in about 50% of the families, suggesting that either mutation in regulatory elements or deletions occur in a significant proportion of cases.

3.3.4 Linkage analysis in familial breast and ovary cancer (p.138 of 1992/93 Biennial report)

Linkage studies have continued in order to reduce the size of the BRCA1 locus. New recombinants have been identified, such as a key one placing BRCA1 distal to the 17-hydroxysteroid dehydrogenase gene (EDH17B2), confirming the exclusion of this gene as BRCA1 (Tonin *et al.*, 1994).

The effort to generate a physical map of the region has continued. Genes have been identified. A special effort was made in analysing an exceptional family in which epidermolytic palmoplantar keratoderma (EPPK) cosegregates with breast and ovarian cancer, raising the possibility that a single genetic mutation might cause these conditions and offering a potential lead to the identification of a hereditary breast/ovarian cancer gene. We have

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performed linkage analysis and shown that the EPPK locus lies on the long arm of chromosome 17 near the type 1 keratin gene cluster and the proposed breast cancer gene (BRCA1). The type 1 keratin 9 gene has been partially sequenced in four affected individuals. A single base mutation within the rod domain of the protein cosegregates with EPPK in all affected individuals tested. Although inheritance of this mutation is probably responsible for EPPK, it is unlikely to be the cause of breast and ovarian cancer (Torchard *et al.*, 1994).

Shortly after the period under review, identification of the BRCA1 gene was announced (Miki *et al.*, 1994).

Professor H. Lynch has been using the typing information provided by the linkage analysis to counsel families (Lynch *et al.*, 1994).

A better estimate of the risks of cancer in carriers of BRCA1 mutations was performed with the Breast Cancer Linkage Consortium (Ford *et al.*, 1994). The study provides estimates of breast and ovarian cancer risks which are useful for counselling BRCA1-mutation carriers. It also shows that carriers are at increased risk of colon and prostate cancer, which may be of clinical significance in certain families if the risks are associated with specific mutations.

Furthermore, analysis of the histology of BRCA1-associated ovarian tumours has shown that BRCA1 mutations are unlikely to predispose to mucinous epithelial ovarian cancer. Our data imply that caution should be exercised when counselling family members of women with mucinous ovarian carcinomas about cancer risks, especially when BRCA1-linked markers are employed (Narod *et al.*, 1994).

Our group has participated in the identification of a second breast cancer susceptibility locus. A consortium headed by M. Stratton and D. Easton (Sutton) was established in order to identify other breast cancer susceptibility loci. A genomic linkage family using 15 high-risk breast cancer families unlinked to BRCA1 on chromosome 17q21 localized a second breast cancer susceptibility locus (BRCA2) to a 6-centimorgan interval on chromosome 13q12-13. Preliminary evidence suggests that BRCA2 confers a high risk of breast cancer but, unlike BRCA1, does not confer a substantially elevated risk of ovarian cancer (Wooster *et al.*, 1994).

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PART 4. RESEARCH ON THE PREVENTION AND EARLY DETECTION OF CANCER

4.1 The Gambia Hepatitis Intervention Study

(p. 143 of 1992/93 Biennial Report)

4.1.1 Monitoring the effect of HBV vaccination

The seventh-year follow-up of a cohort of about 1000 children from the first centres to receive the vaccine has been completed, with 70% of recruited children traced and bled. Of these children, 93% were free of infection, even though antibody levels had decayed below the level originally considered protective in 28% of the children bled. Four children have been confirmed as chronic carriers; one other child was HBsAg-positive at the seventh-year bleed but he has not yet been re-bled to ascertain whether he had a transient infection or is a chronic carrier.

All the data on vaccines received by the GHIS cohort have now been added to the main database, and inconsistencies are being resolved (for example, vaccines recorded before date of birth or second HBV vaccine dose recorded as received before first dose). Foot and palm prints of the GHIS cohort are being photographed on numbered films.

4.1.2 Cancer registration

Strengthening of cancer registration has continued. While the Cancer Registrar is undergoing training in the UK, registration has been carried out by the Assistant Cancer Registrar, and a second Assistant Registrar has recently been appointed. In October 1993 the first of a rotation of pathologists, recruited by Professor Cali of the University of Naples, arrived in The Gambia; the second is currently in post. Yearly cancer incidence estimates for the period July 1986 to June 1993 are consistent and stable. Primary liver cancer is the most common male malignancy, and rates second to cervical cancer in females.

4.1.3 Ancillary studies

No further field work has been carried out in the study of mutant viruses, but laboratory analysis of the sera continues. Statistical analysis of the data from the study on genetic predisposition to antigenaemia is in progress. Some children were HBsAg-positive at the first bleed and need to be re-bled to ascertain whether they are carriers, before the analysis can be completed. Jaundice surveillance has been discontinued as it proved impossible to get reliable information from two of the three traditional healers who were reporting to us.

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4.1 IARC staff publications

DelMistro, A., Chotard, J., Hall, A.J., Fortuin, M., Whittle, H., DeRossi, A. & Chieco-Bianchi, L. (1994) HTLV-I/II seroprevalence in The Gambia: a study of mother-child pairs. *AIDS Res. Hum. Retrovirus*, **10** (5) 6

Fortuin, M., Karthigesu, V., Howard, C., Hoare, S., Mendy, M. & Whittle, H.C. (1994) Break-through infections and identification of a viral mutant in Gambian children immunised with hepatitis B vaccine or evidence of a mutant virus among hepatitis B break-through infections in vaccinated Gambian children. *J. Infect. Dis.* (in press)

Hall, A.J., Robertson, R.L., Crivelli, P.E., Lowe, Y., Inskip, H.M., Snow, S.K. & Whittle, H. (1993) Cost-effectiveness of hepatitis B vaccine in The Gambia. *Trans. R. Soc.Trop. Med. Hyg.*, **87**, 333–336

Hudson, G.J., Wild, C.P., Zarba, A. & Groopman, J.D. (1992) Aflatoxins isolated by immunoaffinity chromatography from foods consumed in The Gambia, West Africa. *Natural Toxins*, **1**, 100–105

Karthigesu, V.D., Allison, L.M.C., Fortuin, M., Mendy, M., Whittle, H.C. & Howard, C.R. (1994) A novel hepatitis B variant in the sera of immunized children. *J. Gen. Virol.*, **75**, 443–448

Vall Mayans, M., Hall, A.J., Inskip, H.M., Lindsay, S.W., Chotard, J., Mendy, M. & Whittle, H.C. (1994) Do bedbugs transmit hepatitis B? *Lancet*, **343**, 761–763

Wild, C.P., Shrestha, S.M., Anwar, W.A. & Montesano, R. (1992) Field studies of aflatoxin exposure, metabolism and induction of genetic alterations in relation to HBV infections and hepatocellular carcinoma in The Gambia and Thailand. *Toxicol. Lett.*, **64**, 455–461

Wild, C.P., Fortuin, M., Donato, F., Whittle, H.C. Hall, A.J., Wolf, C.R. & Montesano, R. (1993) Aflatoxin, liver enzymes and hepatitis B virus infection in Gambian children. *Cancer Epidemiol. Biomarkers Prev.*, **2**, 555–561

4.2 Other studies of primary prevention of cancer

4.2.1 Review of results of chemoprevention trials for cancer (p. 146 of 1992/93 Biennial Report)

With support of a grant from the Europe Against Cancer programme of the EU, a consultant prepared a complete review of on-going and completed chemoprevention studies, as of February 1993 (Buiatti, 1994).

In collaboration with the UICC and the Europe Against Cancer Programme, plans were completed for a review meeting on this topic, to be held at IARC in January 1995.

4.2.2 Chemoprevention trial on precancerous lesions of the stomach in Venezuela (p. 146 of 1992/93 Biennial Report)

A total of 1890 subjects, towards a target of 2200, have been recruited and randomized to antioxidant treatment or placebo up to June 1994. Compliance with treatment has been satisfactory, with 85% of the subjects leaving less than 10% of the capsules. Only 7.2% of the participants have withdrawn from the trial and four subjects presented allergic reactions to the treatment. At base-line examination, the histological diagnoses of the first 1500 subjects are as follows: superficial gastritis 4%; chronic gastritis 42.7%; chronic atrophic gastritis 16.9%; intestinal metaplasia 26.8%; and dysplasia 9.5%.

The base-line samples from 1365 subjects show a progressive increase in plasma pepsinogen (PG) II levels and a progressive decrease in PG I/II ratio with increasing degree of polynuclear and mononuclear infiltrate, gastric atrophy and intestinal metaplasia.

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By using subjects with superficial gastritis and mild/moderate chronic gastritis as controls, the relation of diet and other risk factors to the prevalence of the more advanced precancerous lesions was investigated. The prevalence of dysplasia was inversely associated with number of years of schooling and with fresh fruit consumption, and positively associated with tobacco use. Similar associations were observed for intestinal metaplasia, although they were of borderline significance. Antioxidant vitamin levels have been measured in the plasma of the first 1009 subjects admitted into the trial. The mean plasma levels of ascorbic acid, β-carotene and α-tocopherol were similar to those reported from populations at low risk for gastric cancer, as in the USA and Switzerland, and higher than the levels recorded in China, another high-risk area for stomach cancer. Males had lower levels of ascorbic acid, α-carotene, β-carotene and cryptoxanthin and higher levels of α-tocopherol and γ-tocopherol than females. Current tobacco users had lower plasma levels of ascorbic acid, α-carotene, β-carotene and cryptoxanthin than non-users and regular alcohol drinkers had a decreased plasma level of β-carotene compared with non-drinkers. Consumption of fresh fruits and vegetables was positively associated with the levels of ascorbic acid, β-carotene and cryptoxanthin.

A second eradication trial of *H. pylori* infection involving 80 subjects was carried out. Subjects were randomly assigned to two treatment regimens: (A) colloidal bismuth subcitrate (DeNol), amoxicillin and metronidazole; (B) omeprazole and clarithromycin, for 14 days. Two months after completion of the treatment, the eradication rate was 28% for treatment A and 21% for treatment B. The lower eradication rates in this trial as compared to those obtained in other populations appears to be due either to differences in *H. pylori* strains, including drug resistance, or to frequent re-infection.

4.2.3 Cancer prevention activities of general practitioners

A telephone survey was conducted on a random sample of general practitioners in the Rhône region, as well as among those practising in cities where a cervical cancer screening programme is being set up. This study is assessing current practices both in terms of primary prevention of cancer (smoking, drinking and dietary patterns as well as methods used to inform patients and to lead them to modify their behaviour) and secondary prevention (screening for breast, cervix and colorectal cancer). Evaluation of needs with regard to initial and continuing education is included.

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4.2 IARC staff publications

Buiatti, E., Muñoz, N., Vivas, J., Cano, E., Peraza, S., Carillo, E., Castro, D., Sanchez, V., Andrade, O., Benz, M., de Sanjosé, S. & Oliver, W. (1994) Difficulty in eradicating *Helicobacter pylori* in a population at high risk for stomach cancer in Venezuela. *Cancer Causes Control*, **5**, 249–254

Hakama, M., Beral, V. & Parkin, D.M. (1993) Prevention of digestive cancers — the UICC Project on Evaluation of Primary Prevention. In: Takahashi, T., ed., *Recent Advances in Management of Digestive Cancers* (Proceedings of UICC Kyoto International Symposium on Recent Advances in Management of Digestive Cancers), pp. 38–45

Other articles cited

Buiatti, E. (1994) *Intervention Trials of Cancer Prevention: Results and New Research Programmes* (IARC Technical Report No. 18), Lyon, IARC

4.3 Safe handling of carcinogens and destruction of carcinogenic wastes

4.3.1 Destruction of antineoplastic agents as hospital formulations (p. 148 of 1992/93 Biennial Report)

This work has been initiated in four collaborating laboratories (Frederick Cancer Research Facility, Frederick, MD, USA; Charles University, Prague, Czech Republic; Hôpital St Charles, Montpellier and IARC, Lyon). All the compounds so far tested are degraded with an efficiency of more than 99.9% by 5% sodium hypochlorite or by Fenton reagent. Degradation by 30% hydrogen peroxide was less successful, as several of the compounds (dacarbazine, amsarcesine, azathioprine, vindesine, vincristine, etoposide, teniposide, idarubicin, doxorubicin, daunorubicin) were not efficiently degraded. Residues from degradation are being tested for mutagenic activity.

4.3.2 Safe handling of genotoxic substances (p. 149 of 1992/93 Biennial Report)

A course was organized in Lyon on 30 November–1 December 1993 on safe handling of cytostatic drugs for health workers, and was followed by a practical training session at the Edouard Herriot Hospital (Lyon, France). A second course followed on 2–3 December on the subject of safe handling of genotoxic substances in research laboratories (see Section 6.5.2).

A course was organized in collaboration with the National Cancer Institute (IST) in Genoa on 4–5 November 1993 on safety measures in research laboratories. It was attended by over 50 participants.

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4.3 IARC staff publications

Castegnaro, M. & Rousselin, X. (1994) Cancérogènes, mutagènes chimiques et autres substances toxiques: traitement des déchets avant rejet. In: Rousselin, X., Dayan-Kenigsberg, J., Pleven, C., Castegnaro, M., Picot, A. & Zajdela, F., eds, *Manipulation des Substances Génotoxiques Utilisées au Laboratoire: Prévention et Sécurité*, Paris, Institut National de Recherche et de Sécurité, pp. 26–89

Castegnaro, M. (1994) Methods for the disposal of carcinogens and carcinogenic wastes. In: Purchase, R., ed., *The Laboratory Environment*, Cambridge, Royal Society of Chemistry, pp. 81–113

Dayan-Kenigsberg, J., Pleven, C., Castegnaro, M. & Rousselin, X. (1994) Consignes de prévention et de sécurité lors de la manipulation de substances génotoxiques utilisées au laboratoire. In: Rousselin, X., Dayan-Kenigsberg, J., Pleven, C., Castegnaro, M., Picot, A. & Zajdela, F., eds, *Manipulation des Substances Génotoxiques Utilisées au Laboratoire: Prévention et Sécurité*, Paris, Institut National de Recherche et de Sécurité, pp. 9–17

Lunn, G., Sansone, E.B., De Méo, M., Laget, M. & Castegnaro, M. (1994) Potassium permanganate can be used for degrading hazardous compounds. *Am. Ind. Hyg. Assoc. J.*, **55**, 167–171

Picot, A., Zerbib, J.C. & Castegnaro, M. (1993) Sécurité et prévention: Risques liés à la manipulation des produits cancérogènes. *L'Actualité Chimique*, July–September, 44–49

Zajdela, F., Picot, A., Castegnaro, M. & Rousselin, X. (1994) Liste des principaux produits génotoxiques utilisés dans les laboratoires de recherche français. In: Rousselin, X., Dayan-Kenigsberg, J., Pleven, C., Castegnaro, M., Picot, A. & Zajdela, F., eds, *Manipulation des Substances Génotoxiques Utilisées au Laboratoire: Prévention et Sécurité*, Paris, Institut National de Recherche et de Sécurité, pp. 18–25

4.4 Studies of screening for cancer

4.4.1 Screening for cancer of the breast in the Philippines (p. 150 of 1992/93 Biennial Report)

Following the pilot study, some modifications were made to the study protocol. A research grant that will cover the first five years of this study, through the US Army Medical Research Development Command, has enabled planning for its implementation in January 1995 to begin.

4.4.2 Screening for cancer of the stomach in Latin America (p. 150 of 1992/93 Biennial Report)

The case–control study to evaluate the efficacy of the on-going screening programme for gastric cancer by photofluoroscopy in Tachira province, Venezuela has been completed (Pisani *et al.*, 1994). A study of the relative sensitivity and specificity of serum pepsinogens versus gastric biopsies to classify the histological state of the gastric mucosa has been performed in Venezuela and the results are being analysed.

4.4.3 Screening for cancer of the cervix in developing countries (pp. 150–151 of 1992/93 Biennial Report)

A limited cervical cancer screening programme by Pap smear has been implemented in certain regions of greater Manila over the last 16 years. As part of a case-control study of etiological factors (see Section 2.12.2), information has been collected on the subjects'

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previous screening history and on their knowledge of and attitudes towards screening and preventive health care, in order to evaluate the risk of advanced disease and the magnitude of selection bias in the assessment.

Since organized cervical cytology screening programmes may not be feasible in developing countries, alternative procedures, such as visual inspection of the uterine cervix of asymptomatic women and low-intensity cytology, have been suggested for cervical cancer control. These approaches have not yet been evaluated in community settings for their practicality of implementation, effectiveness in reducing mortality, and cost benefit. Community-based studies have been undertaken in two locations in India to study the sensitivity and specificity of visual inspection by speculum examination in relation to Pap smear. A randomized intervention trial to involve some 80 000 women aged 40–64 years in Trivandrum district (Kerala) has been designed to evaluate visual inspection and low-intensity cytology in terms of reduction in mortality and cost-effectiveness.

4.4.4 Evaluation of oral cancer screening

In Cuba, an on-going oral cancer screening programme offers annual oral visual inspection by dentists to subjects aged 15 years and over. A preliminary evaluation revealed a low compliance with screening and with referral for investigations and treatment. No change has been observed in oral cancer incidence and mortality rates in Cuba since the implementation of the programme. A case–control study is now being conducted to evaluate the risk of advanced oral cancer in relation to screening history.

A randomized intervention trial is planned for implementation in Trivandrum district (Kerala, India) to evaluate oral visual inspection by trained social workers for its effectiveness in reducing incidence and mortality. The proposed community-based study aims to recruit approximately 90 000 subjects aged 40–65 years. Plans have also been developed to evaluate mouth self-examination in the control of oral cancer.

4.4.5 Evaluation of screening for neuroblastoma (p. 151 of 1992/93 Biennial Report)

Following the consensus reached among the participants in the Study Group for the Evaluation of Neuroblastoma Screening in Europe (Estève *et al.*, 1994), it was decided to study the feasibility of screening at 12 months. In the meantime, a detailed study of survival of children with neuroblastoma has been undertaken and should help to refine the previous estimation of the power of various screening trials.

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4.4 IARC staff publications

Cortesina, G., Gabriele, P., Giordano, C., Merletti, F., Morrison, A.S., Mueller Hermelink, H.K., Palestro, G., Sannazzari, G.L., Sartoris, A., Sasco, A.J., Segnan, N., Steiner, W., Succo, G., Terracini, B., Valente, G. & Vershulst, J. (1993) Report of an international workshop on perspectives on secondary prevention of laryngeal cancer. *Eur. J. Cancer*, **29**, 1343–1352

Estève, J., Parker, L., Roy, P., Hermann, F., Duffy, S., Frappaz, D., Lasset, C., Hill, C., Sancho-Garnier, H., Michaelis, J. & Philip, T. (1994) Is neuroblastoma screening evaluation needed and feasible? *Br. J. Cancer* (in press)

Pisani, P., Oliver, W.E., Parkin, D.M., Alvarez, N. & Vivas, J. (1994) Case–control study of gastric cancer screening in Venezuela. *Br. J. Cancer*, **6**, 1102–1105

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PART 5. DEVELOPMENT OF METHODS FOR CANCER RESEARCH

5.1 Methods for measuring and monitoring exposure to particular carcinogens

5.1.1 Development of methods for biological monitoring of exposure to chemical carcinogens that yield DNA etheno-adducts

5.1.1.1 *An ultrasensitive method for the analysis of DNA etheno-adducts* (pp. 153–154 of 1992/93 Biennial Report)

The analysis of 1,N^6-ethenoadenine (εA) and 3,N^4-ethenocytosine (εC) residues in DNA by immunoaffinity purification and ^{32}P-postlabelling of the 3′-nucleotides was validated by comparison with an independent method based on HPLC pre-separation and radioimmunoassay of the etheno-deoxyribonucleosides. Duplicate analyses were done on two DNA samples obtained from pre-weanling rats, one exposed to vinyl chloride and the other unexposed. The results were similar by other methods.

5.1.1.2 *Background levels of DNA etheno-adducts in untreated animals* (pp. 153–154 of 1992/93 Biennial Report)

Background levels of εA and εC were detected in DNA from the liver, lung, kidney and circulating lymphocytes of unexposed, adult Sprague-Dawley rats. The liver had 40 to 70 times less εA and 100 to 180 times less εC than the other tissues examined. However, analysis of liver DNA samples from rats for breeding, fed a powdered diet, revealed 20 to 30 times higher levels of εA and εC, suggesting an effect of diet on the background levels of these adducts.

5.1.1.3 *Formation and persistence of DNA etheno-adducts in rats exposed to vinyl chloride* (p. 155 of 1992/93 Biennial Report)

The study on the formation and accumulation of εA and εC in DNA during prolonged exposure of rats to vinyl chloride has been completed for the liver, lung and kidney. In the liver, both εC and εA accumulate during exposure and persist in liver DNA for up to two months after the end of exposure, showing that they are poorly repaired under these conditions. In contrast, in lung and kidney, only εC accumulates in DNA, whereas εA appears to be efficiently repaired.

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The formation and persistence of etheno-adducts is being measured in DNA of various organs from pre-weanling rats, which are more susceptible to vinyl chloride-induced carcinogenesis.

5.1.1.4 *Formation of DNA ethenobases by lipid peroxidation products* (p. 154 of 1992/93 Biennial Report)

Lipid peroxidation (LPO) products can react *in vitro* with nucleosides or nucleotides to yield ethenobase adducts. To examine whether the stimulation of LPO *in vivo* could lead to the formation of ethenobases in DNA, two animal models of LPO were investigated. In a first series of experiments, Sprague–Dawley rats were submitted to treatments known to stimulate LPO (dietary iron overload and administration of ethanol or carbon tetrachloride). Several organs and blood were collected for the determination of the prooxidant/antioxidant status and of εA and εC levels in DNA. Secondly, etheno-adducts were quantitated in hepatic DNA from Long–Evans rats of different ages: some with a cinnamon-like colour (LEC rats) and then with agouti coat colour (LEA rats). LEC rats have been established as a mutant inbred strain displaying hereditary hepatitis and hepatoma and copper accumulation. LEA rats are a sibling line of LEC rats which do not suffer from liver disease. The data obtained show that higher levels of etheno-adducts in liver DNA are associated with the stimulation of LPO *in vivo*. For example, a three-week treatment with iron fumarate and carbon tetrachloride doubled the level of both ethenobases in liver DNA of rats fed a powdered diet. Hepatic DNA of 18-week old LEC rats exhibited levels of εA and εC that were 30 and 5 times higher, respectively, than in control LEA rats of the same age.

5. 1. 2 Oxidative stress

The habit of betel quid chewing is causally associated with an increased risk of oral cancer. We have demonstrated that hydroxy radicals are formed in the human oral cavity during betel quid chewing, by showing that *o*- and *m*-tyrosine in the saliva are formed from phenylalanine, which was added to the betel quid.

We are developing new methods to measure nitrotyrosine and dityrosine in tissue protein as markers of peroxynitrite-mediated tissue damage and oxidative stress. The formation and metabolism of DNA base-propenals and oxidized or nitrated guanine derivatives, both of which are easily formed by the reaction of DNA with peroxynitrite, are also being studied. These DNA modifications could be measured as an index of NO-induced DNA damage (see Section 2.7.2).

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5.1.3 p53 autoantibodies in lung cancer patients

A study was performed to test whether serum antibodies to p53 protein are a good marker of p53 mutations in lung cancer patients. Among 134 sera, 16 (12%) were positive for antibodies by ELISA. Tumour tissue was available for mutation analysis from 94 of the patients, and 46 tumours showed a mutation, of which seven were from patients with serum p53 antibodies. The possibility that p53 autoantibodies could be an early marker of lung and/or other cancers will be further examined.

5.1.4 Biomonitoring of exposure to the food-borne carcinogen PhIP (p. 157 of 1992/93 Biennial Report)

The cooking of meat induces the formation of a family of structurally-related heterocyclic aromatic amines. One of these compounds, 2-amino-1-methyl-6-phenylimidazo[4,5-*b*]pyridine (PhIP), induces colon tumors in rodents. A sensitive and specific method has been developed to measure levels of PhIP adducted to DNA in tissues. The method, based on a similar approach for DNA adducts of 4-aminobiphenyl (Lin *et al.*, 1994), involves alkaline hydrolysis of PhIP from DNA, followed by gas chromatography/electron capture mass spectrometry. The method can detect PhIP–DNA adducts at levels down to 0.03 fmol PhIP/μg DNA (1 PhIP adduct/10^8 normal nucleotides) for a 100 μg sample. To validate the alkaline hydrolysis– GC/MS method, 20 DNA samples from five tissues of rats treated orally with PhIP were analysed by both GC/MS and ^{32}P-postlabelling. Results from the two methods were highly correlated ($r^2 = 0.83$). With human DNA samples, both alkaline hydrolysis–GC/MS and ^{32}P-postlabelling provided evidence for PhIP–DNA adducts in two out of six colon samples, but not in twelve pancreas samples or six urinary bladder samples (Friesen *et al.*, 1994).

5.1.5 Postlabelling methodology study (pp. 157–158 of 1992/93 Biennial Report)

A series of collaborative studies has been set up, funded by the European Commission, to improve and standardize methodologies for postlabelling of bulky and small DNA adducts. The United States Environmental Protection Agency proposes to join this project and has already organized, in collaboration with the National Cancer Institute and the National Center for Toxicological Research, a biomonitoring working group in which IARC is participating. One of the major tasks of this group is to develop a bank of standard DNA adducts which can be used in collaborative studies and in interlaboratory comparison of biomonitoring methods.

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5.1.6 Validation of methods for fumonisin analysis (p. 158 of 1992/93 Biennial Report)

An evaluation of analytical methodologies for the quantitative determination of fumonisins B_1 and B_2 in maize has been organized, coordinated by the Community Bureau of Reference of the European Commission. Among several published methods, that of Shepard *et al.* (1990) provided the most reproducible results and was thus adopted for the analysis of fumonisins in various food and feed matrixes. The results from the group are being evaluated by the European Commission. This method was applied to a series of maize samples from the Gambia but none contained detectable levels of fumonisins B_1 or B_2 (<50 ng/g).

5.1 IARC staff publications

Bartsch, H., Barbin, A., Marion, M.-J., Nair, J. & Guichard, Y. (1994) Formation, detection and role in carcinogenesis of ethenobases in DNA. *Drug Metab. Reviews*, **26**, 349–371

Durand, M.-J. & Shuker, D.E.G. (1993) Adducts and apurine sites in "probe" DNA as markers of DNA-damaging potential in biological fluids. In: Galteau, M.M., Henny, J. & Siest, G., eds, *Biologie Prospective '8ème Colloque International de Pont-à-Mousson'*, Paris, John Libbey Eurotext (in press)

Friesen, M.D., Kaderlik, K., Lin, D., Garren, L., Bartsch, H., Lang, N.P. & Kadlubar, F.F. (1994) Analysis of DNA adducts of 2-amino-1-methyl-6-phenylimidazo[4,5-b]pyridine in rat and human tissues by alkaline hydrolysis and gas chromatography/electron capture mass spectrometry: Validation by comparison with ^{32}P-postlabelling. *Chem. Res. Toxicol.* (in press)

Lin, D., Lay, J.O., Bryant, M.S., Malaveille, C., Friesen, M., Bartsch, H., Lang, N.P. & Kadlubar, F.F. (1994) Analysis of 4-aminobiphenyl-DNA adducts in human urinary bladder and lung by alkaline hydrolysis and negative ion gas chromatography/mass spectrometry. *Environ. Health Persp.* (in press)

Shuker, D.E.G., Prevost, V., Friesen, M.D. & Bartsch, H. (1993) Non-invasive methods for measuring DNA alkylation in experimental animals and humans. *Environ. Health Perspect.*, **101** (Suppl. 3), 151–153

Other articles cited

Shepard, G.S., Sydenham, E.W., Thiel, P.G. & Gelderblom, W.C.A. (1990) Quantitative determination of fumonisins B_1 and B_2 by high-performance liquid chromatography with fluorescence detection. *J. Liq. Chromatog.*, **13**, 2077–2087

5.2 Human cell transformation

(p. 163 of 1992/93 Biennial Report)

IARC is coordinating a European project on human cell transformation, which is funded partially by the European Union. The collaborators are R. Newbold (Uxbridge, UK), N.E. Fusenig (Heidelberg, Germany), J. Simons (Leiden, The Netherlands) and A. Haugen (Oslo, Norway). The aim is to develop a model system of human cell transformation *in vitro* to study mechanisms of human carcinogenesis, based on our long-term experience of rodent cell transformation studies. We plan to use such a system to study the molecular and cellular mechanisms which make human cells more resistant to cell transformation than rodent

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counterparts, with special emphasis on possible differences in genomic instability and immortalization between these two species.

We used Hu-MI cells (SV40-immortalized human milk epithelial, non-tumorigenic) and HuMI-TTu2 cells (Hu-MI derivative, tumorigenic) for a human cell transformation experiment. TPA inhibited the growth of Hu-MI cells by 95% at 1 ng/ml, but was not toxic to Hu-MI-TTu2 cells even at 1000 ng/ml. When Hu-MI cells were treated with 3-methylcholanthrene, then subcultured in soft agar in the presence of TPA every week, colony formation occurred eight weeks after plating, suggesting that this system may be useful as a model of human cell transformation.

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PART 6. DISSEMINATION OF INFORMATION, AND EDUCATION AND TRAINING IN CANCER RESEARCH

6.1 Publication of information directories on cancer research

6.1.1 *Directory of On-Going Research in Cancer Epidemiology* (p. 166 of 1992/93 Biennial Report)

The Directory, published annually since 1976 and biennially since 1992, is a compilation of on-going, unpublished studies in cancer epidemiology, with eight indexes (by investigator, key-word, cancer site, study type, chemical, occupation, country and cancer registry). The 1994 Directory contains information on 1246 projects being conducted in 80 countries by 876 investigators. The main feature of this volume is the increasing interest in genetic epidemiology, intervention studies, infections and cancer, and biomarkers.

A CD-ROM publication with the entire content of the Directory is in the final stage of preparation (see Section 6.1.3).

6.1.2 *Directory of Agents Being Tested for Carcinogenicity* (p. 166 of 1992/93 Biennial Report)

The *Directory of Agents Being Tested for Carcinogenicity* (formerly Information Bulletin on the Survey of Chemicals Being Tested for Carcinogenicity) was initiated in 1973 in collaboration with the US National Cancer Institute. The Directory of Agents No. 16, published in June 1994, gives information on 580 chemicals or agents being tested in 75 institutes in 23 countries; a total of 243 published reports on 208 chemicals or agents are listed. Each entry gives the name, Chemical Abstracts Registry Number and synonyms for the chemical, use category, purity, species, strain, sex and number of animals, route of administration and dose levels, duration, starting date, stage of experiments and principal investigator.

Analysis of the data reported in Directories Nos 14, 15 and 16 shows that the number of carcinogenicity studies being undertaken in each two-year period appears to be diminishing.

6.1.3 **Electronic publication** (p. 167 of 1992/93 Biennial Report)

A range of information resources produced by IARC will be made available electronically on a CD-ROM (compact disc, read-only memory). This IARCancerDisc contains the full series of IARC Monographs (Vols. 1–55), the *Directory of On-Going*

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Research in Cancer Epidemiology, the *Directory of Agents Being Tested for Carcinogenicity*, the IARC/EPA Genetic Activity Profile database and cancer incidence and mortality data for 1978–87. A structured database containing subsets of information from the IARC Monographs is also included to allow more rapid and efficient searching than can be achieved by free-text searching alone. Standardized index terms for chemical class, use, species, target organs, tumour types, mutagenicity and reproductive effects are given. The CD-ROM is published by SilverPlatter Information, Inc., and a discounted subscription price is available for purchasers in developing countries.

6.2 Other scientific publications

(p. 166 of 1992/93 Biennial Report)

New publications that have appeared during the period under review are the following:

IARC Monographs on the Evaluation of Carcinogenic Risks to Humans. Volume 57, *Occupational Exposures of Hairdressers and Barbers and Personal Use of Hair Colourants; Some Hair Dyes, Cosmetic Colourants, Industrial Dyestuffs and Aromatic Amines*

IARC Monographs on the Evaluation of Carcinogenic Risks to Humans. Volume 58, *Beryllium, Cadmium, Mercury and Exposures in the Glass Manufacturing Industry*

IARC Monographs on the Evaluation of Carcinogenic Risks to Humans. Volume 59, *Hepatitis Viruses*

Pathology of Tumours in Laboratory Animals. Vol. 2, *Tumours of the Mouse* (IARC Scientific Publications No. 111)

Time Trends in Cancer Incidence and Mortality (IARC Scientific Publications No. 121)

International Classification of Rodent Tumours. Part I. *The Rat* (IARC Scientific Publications No. 122) (fascicles 4–7)

Postlabelling Methods for the Detection of DNA Damage (IARC Scientific Publications No. 124)

DNA Adducts: Identification and Biological Significance (IARC Scientific Publications No. 125)

Butadiene and Styrene: Assessment of Health Hazards (IARC Scientific Publications No. 127)

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Directory of On-going Research in Cancer Epidemiology 1994 (IARC Scientific Publications No. 130)

Cancer in the African Population of Bulawayo, Zimbabwe, 1963–1977: Incidence, Time Trends and Risk Factors (IARC Technical Reports No. 15)

Cancer in Thailand 1988–1991 (IARC Technical Reports No. 16)

Intervention Trials for Cancer Prevention: Results and New Research Programmes (IARC Technical Reports No. 18)

Comparability and Quality Control in Cancer Registration (IARC Technical Reports No. 19)

Epidémiologie du cancer dans les pays de langue latine (IARC Technical Reports No. 20)

ICD Conversion Programs for Cancer (IARC Technical Reports No. 21)

Directory of Agents Being Tested for Carcinogenicity No. 16

6.3 Organization of scientific meetings

6.3.1 Conference on Interactions of Cancer Susceptibility Genes and Environmental Carcinogens, 9–13 November 1993 Lyon, France

Recent advances in molecular biology have created new opportunities to identify and control the causes of human cancers. To summarize current knowledge and explore future research opportunities, an interdisciplinary conference was held under the joint sponsorship of the International Agency for Research on Cancer and the American Association for Cancer Research, and supported by grants from the Commission of the European Communities, the Ligue Nationale Française contre le Cancer, and the National Institute of Environmental Health Sciences (USA). An international panel of experts presented papers covering the following topics: human cancer epidemiology; biomarkers of individual susceptibility; mechanisms of transgenerational carcinogenesis; experimental models of genetic susceptibility; genetic instability; and DNA damage and repair. A total of 78 posters were also presented, with the participation of many young investigators.

6.3.2 International conference on retrospective assessment of occupational exposures in epidemiology, 13–15 April 1994, Lyon, France

Retrospective exposure assessment is a field of epidemiology that has experienced interesting advances during the last decade. New approaches have been proposed and applied, particularly in the assessment of occupational exposures, as a result of collaboration between epidemiologists and industrial hygienists. A second international conference, organized by the

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International Agency for Research on Cancer in collaboration with the US National Institute for Occupational Safety and Health and the US National Cancer Institute, and with support from the European Commission, Directorate General XII, was attended by over 200 participants. Four invited lectures and 30 proffered papers addressed issues related to retrospective exposure assessment in community- as well as industry-based studies, the use of biomarkers of exposure, the choice and validation of measures of exposure, and theoretical aspects of exposure assessment. A total of 71 posters were also presented.

6.3 IARC staff publications

Li, F.P. & Montesano R. (1994) Meeting Report. Interactions of Cancer Susceptibility Genes and Environmental Carcinogens, American Association for Cancer Research (AACR) - International Agency for Research on Cancer (IARC) Joint Conference. *Cancer Res.*, **54**, 4243–4247

6.4 Cancer research awards

6.4.1 IARC Research training fellowships (pp. 171–174 of 1992/93 Biennial Report)

Fellowships have been awarded to 14 out of the 63 candidates evaluated by the Fellowships Selection Committee. These include five in the field of cell biology, one in cell genetics, four in epidemiology (one for basic training), one in pathology and three in viral carcinogenesis. Five of these fellowships are tenable in the USA, three in the UK and one each in Australia, France (IARC), Japan, Norway, Sweden and Switzerland. This programme receives support from the Italian Association for Research on Cancer.

6.5 Conduct of training courses

6.5.1 Detection of health hazards in human populations exposed to mutagens and carcinogens, 15–26 November 1993, Bangkok, Thailand

This course was the fifth of its kind. The Chulabhorn Research Institute hosted the course and provided excellent facilities. This course was organized in collaboration with the United Nations Environment Programme (UNEP), the International Programme on Chemical Safety (IPCS), the International Labour Office and FINNIDA. Drs H. Vainio and C. Wild from IARC coordinated the scientific programme. There were 36 participants coming from Egypt, Hong Kong, India, Indonesia, Kuwait, Malaysia, Myanmar, People's Republic of China, Philippines, Singapore, Tanzania and Thailand.

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6.5.2 **Safe handling of cytostatic drugs for health workers and Safe handling of genotoxic substances in laboratory work,** 30 November –1 December and 2–3 December 1993, Lyon, France

These courses were organized, as on previous occasions, in collaboration with the French National Institute of Research and Safety (INRS). The first course was for advanced training for nurses and public health workers, the second more specifically for engineers and occupational health officers. The programme coordinators were Dr M Castegnaro from IARC and Dr X. Rousselin from INRS. Approximately 60 participants attended the two courses.

6.5.3 **Scientific communication,** 13–26 December 1993, Lyon

This course was designed for IARC scientific staff, with the aim of assisting them in presenting their findings clearly, concisely and convincingly. It concentrated on the structure of a scientific paper.

6.5.4 **Introductory course on epidemiology,** 31 May –10 June 1994, Fajara, The Gambia

The course was open to medical doctors, as well as to other health-related professionals with an interest in initiating or pursuing work in cancer epidemiology. The emphasis was on methods of cancer epidemiology and the epidemiological characteristics of cancer in Africa, including measurement of cancer occurrence, determination of cancer causes and evaluation of the effectiveness of preventive measures. The programme coordinator was Dr A.J. Hall, from the London School of Hygiene and Tropical Medicine. The course was attended by 27 students originating from 11 sub-Saharan African countries (Cameroon, Congo, The Gambia, Ghana, Guinea Conakry, Ivory Coast, Mozambique, Nigeria, Sierra Leone, Uganda, Zimbabwe).

6.5.5 **European Educational Programme in Epidemiology—7th residential summer course,** 27 June–15 July 1994, Florence, Italy

For this year's session, there were 60 participants from 23 countries. Dr R. Saracci from IARC was the Course Director.

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Annex 1

STAFF AT IARC
1 July 1993 – 30 June 1994

Office of the Director

Director, IARC	Dr L. TOMATIS (until 31.12.93) Dr P. KLEIHUES (from 1.1.94)
Deputy Director	Dr B.K. ARMSTRONG (until 31.12.93)
Special Adviser on Biostatistics	Dr J. ESTEVE
Administrative assistant	Mrs E. RIVIERE
Secretaries	Mrs C. DECHAUX Miss A. DUFOURNET Mrs W. FEVRE-HLAHOLUK Mrs A. RIVOIRE

Computing Service Group

Head/Computer systems manager	Mr M. SMANS
Computer analyst/System manager	Mr P. DAMIECKI
Scientific software manager	Ms B. CHARNAY
Programme analyst	Mr X. NGUYEN-DINH (until 30.11.93)
Computer operator	Mrs B. KAJO

Gambia Hepatitis Intervention Study

Project leader/Epidemiologist	Dr A. JACK
Project coordinator	Dr R. MONTESANO
Statistician/Programmer	Mr N. MAINE
Secretary	Miss S. COTTERELL
Assistant (Computing)	Miss H. RENARD

Editorial and Publications Service

Head, Editorial & Publications Service/Editor	Dr J. CHENEY
Laboratory technician (Photography)	Mr G. MOLLON

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Clerks	Mr J. DECHAUX Mrs M. MAINAUD (half-time) Mrs A. ROMANOFF Mrs J. THEVENOUX

Library

Librarian	Miss H. MIIDO
Technical assistant (search analyst)	Mrs M. COUDERT
Assistant (Library)	Mrs L. OSSETIAN

Division of Scientific Activities

Unit of Analytical Epidemiology

Chief	Dr R. SARACCI
Scientists	Dr P. BOFFETTA Dr E. CARDIS Mr R. KAAKS Dr E. KOGEVINAS Dr J. LITTLE Dr E. RIBOLI (Head, Programme of Nutrition and Cancer) Dr A.J. SASCO (from INSERM, on special assignment to IARC) Dr N. SLIMANI (from 1.1.94)
Assistants (Statistics)	Mr G. FERRO Mr B. HEMON Miss R. WINKELMANN Mrs A. ARSLAN Miss C. CASAGRANDE (from 1.1.94) Mr D. COLIN (from 8.7.93)
Secretaries	Mrs B. ANDRIEUX (half-time) Mrs A. HANSS-COUSSEAU Miss S. HAVER Miss A. SHANNON Mrs S. SOMERVILLE Mrs S. STALLARD

Unit of Field and Intervention Studies

Chief	Dr N. MUÑOZ
Scientist	Dr F.X. BOSCH (until 1.9.93)
Assistant (Courses)	Mrs M. DAVIS

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Assistants (Statistics)	Miss M. BENZ Miss D. MAGNIN Mr M. ROSATO
Secretary	Mrs H. LORENZEN-BIEHE

Unit of Descriptive Epidemiology

Chief	Dr D.M. PARKIN
Scientists	Dr J. ZIEGLER (Uganda) (from 5.4.94) Dr R. SANKARANARAYANAN Dr P. PISANI
Technical officer	Miss S. WHELAN
Assistants (Statistics)	Mr J. FERLAY Mr E. MASUYER Mr S. OLIVIER
Technical assistant	Mrs E. DEMARET
Secretaries	Miss O. BOUVY Miss M. GEESINK
Clerk	Mrs F. PETIT (half-time)

Unit of Environmental Carcinogens and Host Factors (dissolved)

Chief	Dr H. BARTSCH (until 30.9.93)
Scientists	Dr S. CALMELS-ROUFFET (until 31.12.93) Dr I.K. O'NEILL (until 31.12.93) Dr D. SHUKER (until 1.10.93)
Laboratory technician	Mr P. THUILLIER (until 31.12.93)

Unit of Endogenous Cancer Risk Factors (from 17.1.94)

Chief	Dr H. OHSHIMA
Scientists	Dr C. MALAVEILLE Dr B. PIGNATELLI
Laboratory research assistant	Mrs I. BROUET
Laboratory technician	Mrs A. HAUTEFEUILLE
Secretary	Mrs E. BAYLE

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